DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL TUBULIN INHIBITORS AS ANTICANCER AGENTS

For Partial Fulfilment of
Degree of
Doctor of Philosophy

In the Field of
PHARMACEUTICAL SCIENCES

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INTRODUCTION

The need for new and potent chemotherapeutic drugs with multitargeted activity and low to no damage to normal cells is driven by the high cancer incidence and expensive therapy. The anticancer potential of several novel compounds with natural and synthetic origins has been thoroughly studied. Microtubules have been discovered as prospective targets for anticancer medicines. (1)

The two most significant members of tubulin, α-tubulin and ß-tubulin, construct the long, hollow cylinders known as microtubules. A number of cellular processes, including intracellular transport, cell polarity, shape, signalling, mitosis, cellular integrity, and gene expression, depend on these proteins, which are dynamic filaments of the cytoskeleton. The vinca domain, the taxane binding site, and the colchicine-binding site are the three explicitly identified binding sites on microtubules. The surface of ß-tubulin has these binding sites. (1)

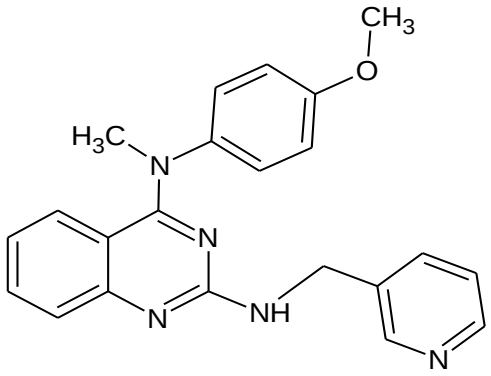
Quinazolines (1,3-benzodiazine) are a type of heterocyclic aromatic nitrogen-containing chemicals that exhibit one of the broadest ranges of activity. Quinazolines can also show apoptotic traits in cancerous cell lines by acting as tubulin inhibitors. (2)

Using the Tubulin Polymerization Assay technique, the antitubulin activity of the generated compounds will be evaluated. Using the tubulin polymerization assay kit, the tubulin polymerization assay will be carried out in accordance with the manufacturer's instructions. (Cytoskeleton based on OD) (3)

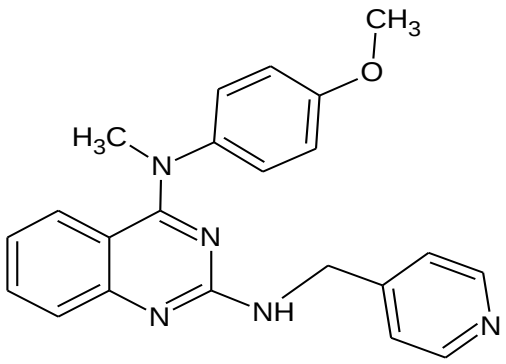
The anti-proliferative and cytotoxic effects of the target molecule on human cancer cell lines and normal human cells, respectively, were investigated using the MTT test. (3)

BRIEF REVIEW OF THE PREVIOUS WORK

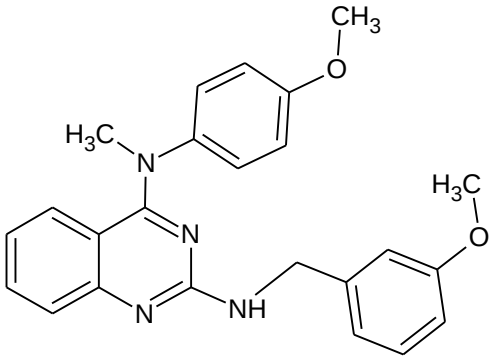
1. W Li, et al in 2018 synthesized and evaluated new quinazolines derivatives as tubulin inhibitor anticancer agents. Compound-1, 2, 3 & 4 was found to be most active. (7)



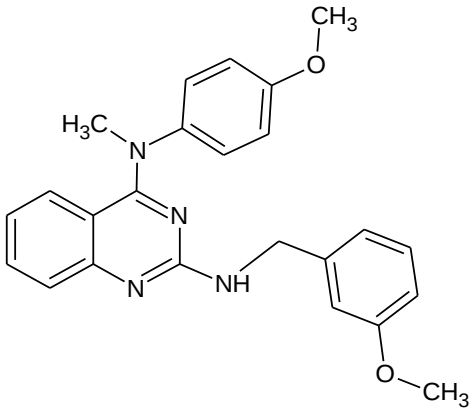
Compound-1



Compound-2

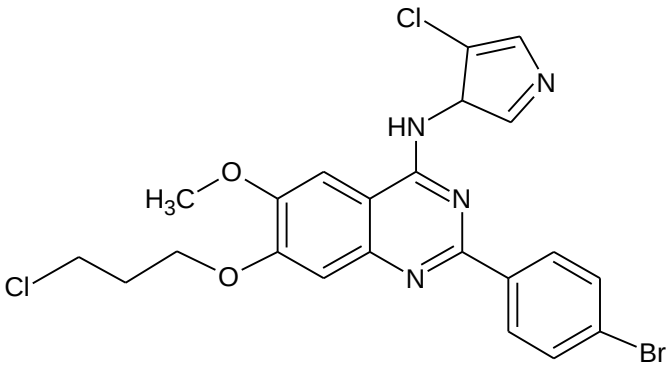


Compound-3

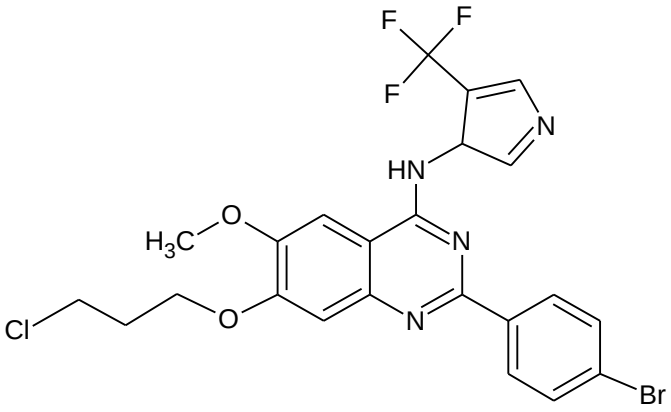


Compound-4

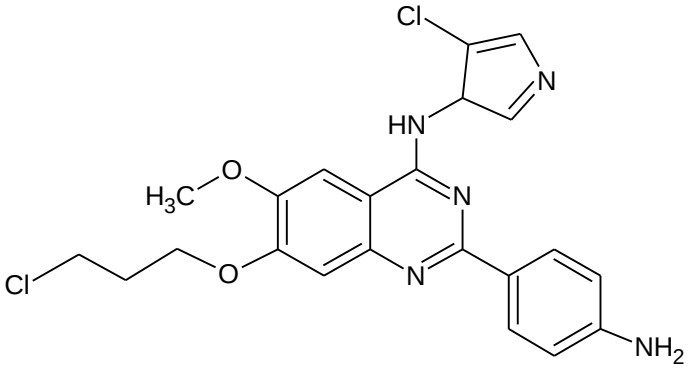
2. Raju Bathula, et al in 2020 synthesised and evaluated 2-substituted 4-anilinoquinazolines for Anti-Cancer Activity.Compound 5, 6, 7 & 8 was found to be most active. (8)



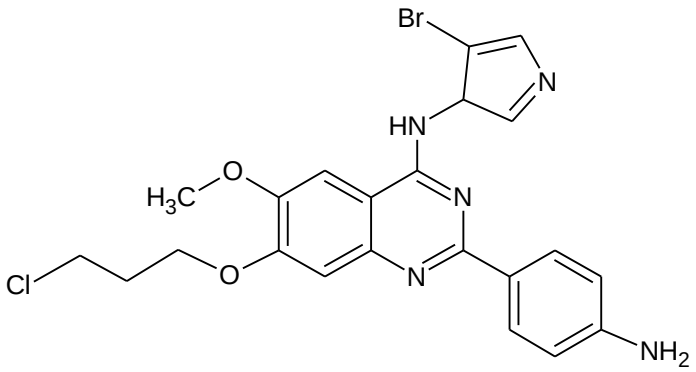
Compound-5



Compound-6

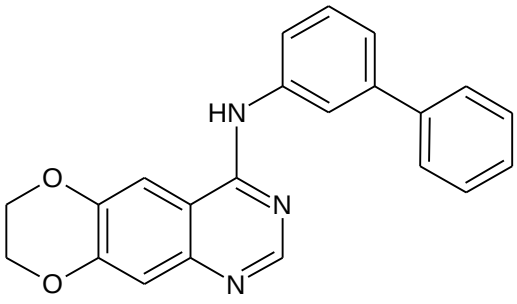


Compound-7

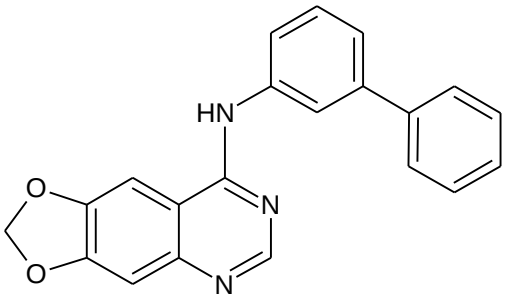


Compound-8

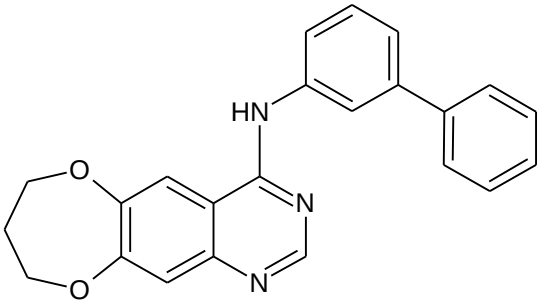
3. Giovanni Marzaro, et al in 2014 synthesised and evaluated Biarylaminoquinazolines as Novel Tubulin Polymerization Inhibitors. Compound 9, 10 & 11 was found to be most active. (6)



Compund-9



Compound-10



Compound-11

OBJECTIVE OF RESEARCH

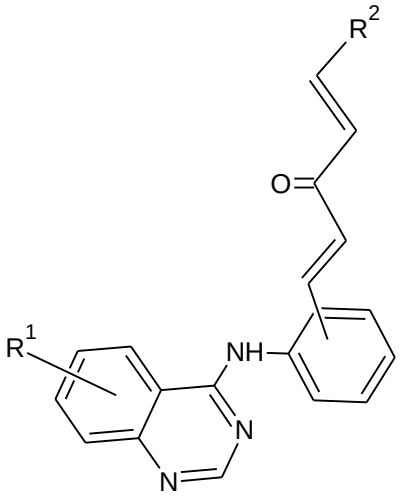
In both industrialised and developing nations, cancer continues to be a serious public health concern. To treat human cancer, wide ranges of cytotoxic medicines with various modes of action are currently used, either alone or in combination. In addition, several substances are in various stages of clinical studies. However, the survival advantages of these medications are not as good as they could be, necessitating a more imaginative treatment or fresh compounds.

Quinazolines and their derivatives are a novel class of cancer chemotherapeutic drugs that have recently gained attention for their promising effectiveness against several tumour types. In addition to offering ideas on the development of novel quinazoline derivatives as anticancer drugs in the near future, this research aims to develop new quinazoline derivatives as tubulin inhibitors for anticancer activity.

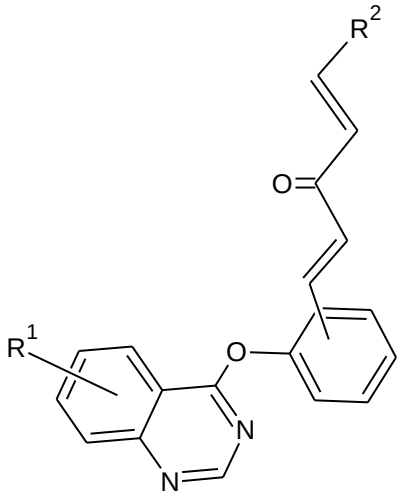
METHODOLOGY OF THE RESEARCH WORK

1. Schemes for the synthesis of compounds

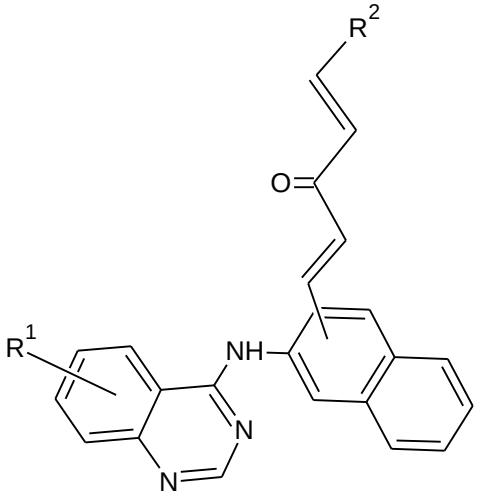
Following Compounds are proposed to be synthesized by using two schemes –



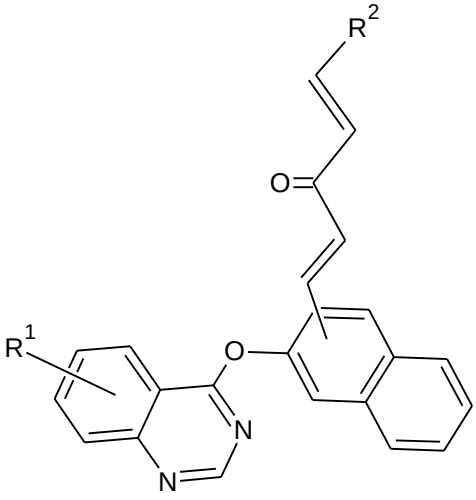
Compound-1



Compound-2



Compound-3



Compound-4

The above compounds will be synthesized by using alkyl substituted 2-Amino benzoic acid with other reagents. The derivatives of above compounds will be synthesised.

2. **Designing of thecompounds**

Molecular modelling software will be used to create analogues of the proposed methods (By using Forge and Flare tools of Cresset Software). Molecular field alignment studies and molecular docking experiments will be utilised to create analogues (at the site of colchicine binding for tubulin protein).

3. **Synthesis of designedanalogues**

Synthetic approaches mentioned in the schemes will be used to create designed analogues.

4. **Purification and characterization of the synthesized compounds**

Purification of the synthesised chemicals will be accomplished using column chromatography or recrystallization. Elemental analysis, Mass Spectroscopy, ^{1}H and ^{13}C NMR and Infrared will be used to characterize them.

5. **Antitubulin activity of the synthesizedcompounds**

The Tubulin Polymerization Assay technique will be used to screen the synthesized compounds for antitubulin activity.

6. **In vitro anticanceractivity**

The antitubulin activity of synthesised compounds will be tested for anticancer activities using a modified MTT assay technique.

EXPECTED IMPACT ON ACADEMICS/INDUSTRY

Proposed research work may lead to the identification and synthesis of some potent anticancer agents which can be used as lead for future research or can be developed further for the treatment of cancer.

SCHEDULE OF ACTIVITIES (PERT CHART)

S. No.	Activity	Time in Months
1.	Designing of Compounds	06 Months
2.	Validation of Schemes	06 Months
3.	Synthesis of Compounds	06 Months
4.	Purification, Structure Elucidation	06 Months
5.	Biological Evaluation	06 Months
6.	Paper Publication and Thesis Writing	06 Months

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